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# An expedient strategy for the diversity-oriented synthesis of macrocyclic compounds with natural product-like characteristics

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ABSTRACT

Naturally-derived macrocyclic compounds are associated with a diverse range of biological activities, including antibacterial effects, and there are over 100 marketed macrocycle drugs derived from natural products. However, synthetic macrocycles are widely considered to be poorly explored in antibiotic development (indeed, within drug discovery in general). This has been attributed to challenges associated with the generation of such compounds. Whilst there are synthetic methods that can produce large collections of structurally similar macrocycles (i.e., compounds with varying appendages based around similar core macrocyclic ring architectures) there is a relative dearth of strategies for the efficient generation of more structurally diverse macrocycle collections in which there is greater variation in the nature of macrocyclic scaffolds present. Such macrocycle collections should contain compounds with a broad range of biological activities (including antibacterial activities) and the requisite robust synthetic methodology useful for analogue synthesis and lead optimization once an active compound has been identified in a biological screen. Herein, we describe a new and expedient diversity-oriented synthesis (DOS) strategy for the generation of a library of novel structurally diverse macrocyclic compounds with a high level of scaffold diversity. The strategy is concise, proceeds from readily-available starting materials, is modular in nature and features a variety of macrocyclisation techniques. In this proof-of-concept study, the synthesis of several previously unreported macrocyclic compounds was achieved. Each of these macrocycles was based around a distinct molecular scaffold and contained natural product-like structural features (e.g., three-dimensionality and multiple hydrogen bond donors and acceptors) as well as synthetic handles for potential further elaboration. The successful generation of these macrocycles demonstrates the feasibility of the new DOS strategy as a synthetic platform for library generation.


## 1. Introduction

The inexorable rise in antibiotic-resistant bacteria has led to a steady decline in the efficacy of existing therapies for the treatment of bacterial infections.[1,2] Moreover, the pace at which new antibacterial agents are being generated has decreased dramatically in recent decades, a legacy of insufficient investment in fundamental antibacterial research by pharmaceutical companies since the 1960s.[1,2] Consequently, humanity is facing the very real and disturbing possibility of a future without an effective method for the treatment of some common bacterial infections.[1,2] Thus, there is a clear and critical medical need for the discovery of novel antibiotics.[1,3]

Lead compounds for antibacterial chemotherapy can be obtained from two sources: nature (natural products) or de novo chemical synthesis.[1] Historically, nature has been by far the more important; most of the major classes of antibiotics in therapeutic use are natural products or semi-synthetic derivatives thereof.[1,3] Among these, a macrocyclic scaffold (a ring system of 12 or more atoms) is common (Fig. 1). Indeed, naturally-derived macrocycles constitute a large class of compounds with useful antibacterial properties.[4–6] Natural macrocyclic derivatives are also associated with a broad range of other attractive biological effects (including anticancer, antifungal and immunosuppressive activities)[5,7] and there are more than 100 marketed macrocyle drugs derived from natural products.[8] The diverse and interesting biological activities associated with the macrocyclic compound class has been attributed to characteristic structural features.[7,8] Their cyclic structure means that they have less conformational freedom than an equivalent acylic compound and so suffer a smaller entropic loss upon

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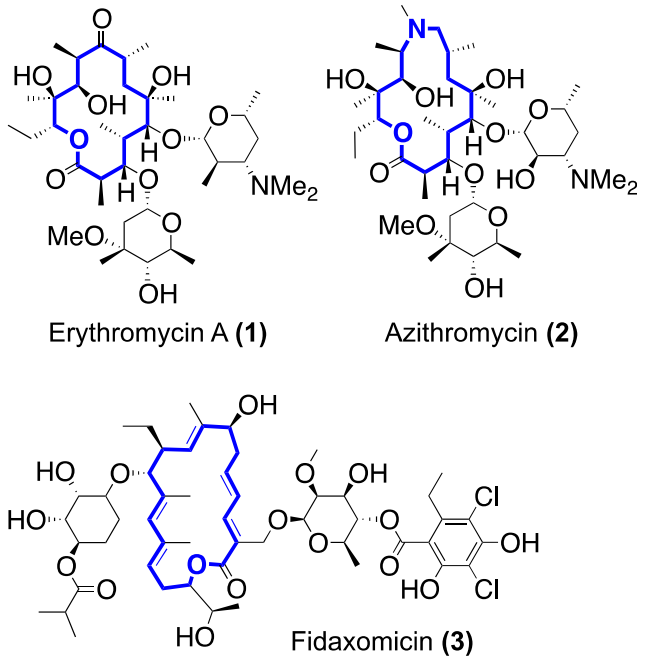



**Fig. 1.** Some examples of naturally-derived antibiotics which are based around macrocyclic scaffolds (highlighted in bold). Erythromycin A **(1)** and Fidaxomicin **(3)** are natural products and Azithromycin **(2)** is a semi-synthetic compound.[5]

binding to a biological target.[7–9] However, unlike smaller cyclic systems, macrocycles retain a certain flexibility, allowing them to potentially mould to a target surface in order to maximize binding interactions.[7–9] In addition, macrocycles can potentially adopt conformations in which polar motifs are buried away, leading to improved membrane permeability relative to their linear analogues.[7]

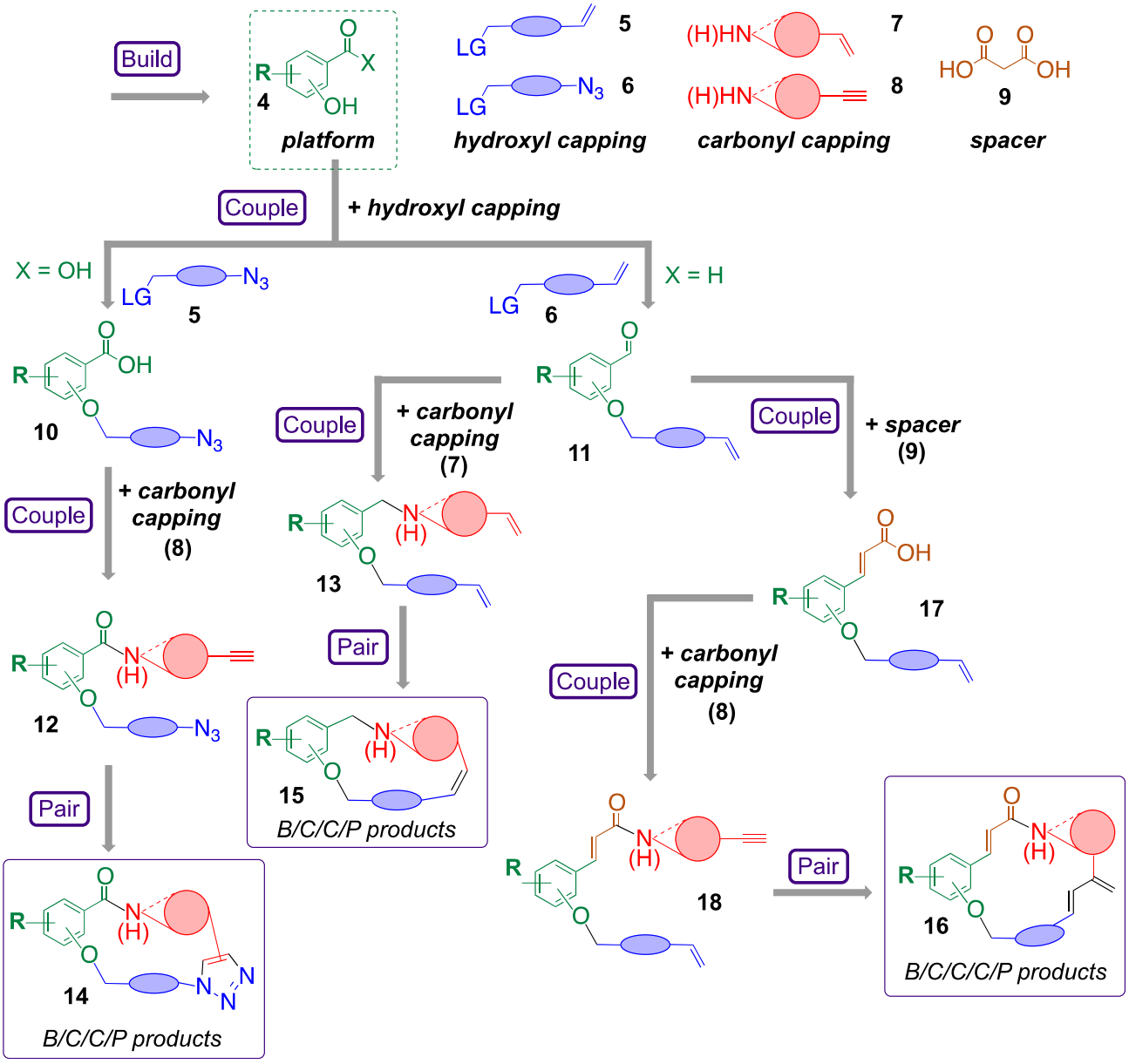
Clearly, macrocycles represent attractive targets in the search for new lead compounds for antibiotic development (indeed, drug development in general).[4,7,8] However, naturally occurring macrocycles are often highly complex in structure, which hampers their synthetic modification and pharmacokinetic optimization.[4,7,10] Thus, attention has shifted in recent years towards the exploration of synthetic macrocycles of medium complexity in drug discovery.[7,10] There has been notable success in this field, with many biologically active synthetic macrocycles with appropriate pharmacokinetic profiles identified[10] (including antibacterial lead compounds[11,12]). However, despite these encouraging examples, synthetic macrocycles are still widely considered to be relatively underexplored within drug discovery in general.[7–10,13] This has been attributed to challenges associated with the synthesis of such compounds, particularly in the context of the formation of the macrocyclic ring architecture.[7,9] Where present in a small molecule, the macrocyclic ring is generally considered to serve as the molecular scaffold (i.e., the core rigidifying structural feature of a molecule).[14] Whilst there are synthetic methods that can produce large collections of structurally similar macrocycles (i.e., compounds with varying appendages based around similar core macrocyclic scaffolds) there is a relative dearth of strategies for the efficient generation of more structurally diverse macrocycle collections in which there is greater variation in the nature of macrocyclic scaffolds present.[10,14] This is a crucial issue in the context of biological screening, since the overall structural, and thus functional diversity of a compound set (i.e., the range of biological activities displayed by the compounds) is known to be highly dependent upon the variety of molecular scaffolds present (the scaffold diversity) of the collection.[15–17] Macrocyclic collections with higher levels of scaffold diversity would be expected to provide a higher hit rate against a broader range of targets than libraries with lower scaffold, and thus overall structural, diversity.[14,15] Scaffold diverse macrocycle collections would therefore be expected to be particularly valuable in biological screens where the nature of the biological target is unknown (e.g., in phenotypic screening).[15,18] In addition, efficient access to structurally diverse macrocycles necessitates the development of synthetic methodology which is robust and broadly applicable in nature, which should facilitate the lead optimization process once a hit compound has been identified.[11,19]

Diversity-oriented synthesis (DOS) is a field of organic chemistry directed towards the efficient generation of molecular libraries that incorporate high degrees of structural diversity, including scaffold diversity.[15,20–22] The screening of DOS libraries has led to the identification of numerous novel biologically active small molecules, including several with antibacterial activities.[3,15,23–28] Recent years have seen the development of several DOS-type strategies specifically targeted at macrocyclic structures including examples from our own research group.[9,10,14,19,27,29–33] However, there remains considerable scope for further developments in the field. From a synthesis perspective, there are improvements that can be made in terms of the expediency of library construction and the efficiency in which scaffold diversity is generated.[19] In addition, large areas of macrocyclic chemical space, that may contain molecules with exciting biological properties (e.g., critically needed new antibacterials), still remain under-explored. These considerations highlight the need for new and expedient DOS strategies towards previously undescribed macrocyclic compounds. Herein, we describe work towards the development of one such strategy, which is based around the use of readily-accessible phenolic carbonyls as key starting materials. In a proof-of-concept study the synthesis of several structurally diverse and previously unreported macrocyclic scaffolds was achieved, which provides a validation of this DOS strategy as a synthetic platform for library generation.

## 2. Results and discussion

### 2.1. Outline of the synthetic strategy

Many DOS pathways are based around a three-phase build/couple/pair (B/C/P) algorithm.[20] In the *build* phase, starting materials (or building blocks) are synthesized. These are then combined (coupled together) in the *couple* phase to yield densely functionalized substrates for the subsequent *pair* phase, which involves intramolecular reactions that join pairwise combinations of functional groups to generate distinct molecular scaffolds.[14,20] In recent years, the use of iterative *couple* steps (i.e., B/C/C/P, B/C/C/C/P, etc.) has been exploited as a means to increase the diversity of scaffolds accessible from a given set of building blocks.[14,34] For example, we have recently reported a DOS strategy towards macrocyclic peptidomimetic scaffolds that incorporates iterative *couple* steps.[14] It was thought that the iterative *couple* concept could be used as the basis for a new and expedient DOS strategy towards novel and diverse macrocyclic compounds. We conceived the use of readily-accessible phenolic compounds of the general form **4**, which bear an electrophilic carbonyl group and a nucleophilic hydroxyl group, as key starting materials (Scheme 1). It was hoped that each given aromatic compound would serve as a 'platform' onto which different building blocks (generated in the *build* phase of the DOS) could be attached through functionalisation of these two reactive sites (*couple* stages). This would then afford a range of distinct acyclic precursors, which could then undergo intramolecular reactions to furnish different macrocyclic compounds, each based around a distinct molecular scaffold (*pair* phases). More specifically, we envisaged the use of four general types of building blocks: the




**Scheme 1.** Outline of the DOS strategy towards structurally diverse macrocyclic compounds of the general forms **14**–**16**. The shaded shapes represent scaffold-defining elements (i.e., regions that can be varied to obtain different macrocyclic scaffolds). LG=a leaving group (e.g., a halogen).

aforementioned aromatic 'platform' building blocks **4** (which would contain an aldehyde or a carboxylic acid moiety together with the hydroxyl group), together with 'hydroxyl capping' building blocks **5** and **6** 'carbonyl capping' building blocks **7** and **8** (cyclic and acyclic amines in both cases) and malonic acid **(9)**, a 'spacer' building block. It was anticipated that the 'platform' aromatic building blocks **4** could be functionalised at the hydroxyl position (a *couple* phase) by reaction with the appropriate 'hydroxyl capping' building block **5** or **6** to furnish compounds of the general form **10** and **11** (from aromatic carboxylic acids and aromatic aldehydes, respectively, Scheme 1). Subsequent functionalisation of the carbonyl moieties with the appropriate 'carbonyl capping' building block **7** or **8** (a *couple* phase) would generate compounds of the general form **12** (by amide bond formation from **10**) and **13** (by reductive amination from **11**). Compounds of the form **12** and **13** contain functional groups that could then potentially be reacted together intramolecularly in the subsequent *pair* phase of the DOS to access diverse macrocyclic scaffolds (B/C/C/P pathways). Specifically, compounds **12** contain a terminal alkyne and terminal azide group; it was envisaged that a regioselective metal-catalysed 'click'-type 1,3-dipolar cycloaddition would thus furnish macrocyclic architectures of the general form **14** containing either 1,5-disubstituted triazoles (ruthenium catalysis) or 1,4-disubstituted triazoles (copper catalysis).

In the case of compounds **13**, which contain two terminal alkene moieties, it was hoped that an intramolecular ring-closing metathesis reaction could be carried out to yield macrocyclic scaffolds of the general form **15**. Furthermore, it was envisaged that larger-sized macrocyclic structures **16** could be accessed by extension of the aldehyde moiety of key branch–point compounds **11** by an additional *couple* step with the 'spacer' building block **9** (a Knoevenagel condensation) to form compounds **17**. Subsequent carbonyl capping with building blocks **8** would generate compounds **18** which contain a terminal alkene and a terminal alkyne. Ring-closing ene-yne metathesis would then furnish the target compounds **16** (the *pair* stage). This would formally constitute a B/C/C/

C/P pathway. These larger-sized macrocycles may be better able to target extended binding interfaces (such as those associated with protein–protein interactions) than the smaller-sized compounds resulting from a single *couple* step.[14,35] Overall, we anticipated that the DOS strategy outlined in Scheme 1 would allow access to novel and structurally diverse macrocyclic compounds of three different structural forms **14**–**16**. Several attractive features of the proposed DOS strategy were identified. It is step-efficient from readily available building blocks. Furthermore, it is inherently modular in nature. Thus, it was anticipated that high levels of structural diversity could be achieved in an expedient fashion through the use of a small set of building-blocks. Variation in the scaffold-defining elements of the building blocks should allow for efficient generation of scaffold diversity within each general structural form, as well as providing scope for the installation of diverse achiral and chiral appendages and potential biomolecular-interacting elements around the core macrocyclic ring architectures. The use of different macrocyclisation techniques in the DOS should also offer an expansion in the number of distinct molecular scaffolds accessible from a given set of building blocks (relative to strategies which employ only one method of ring-closure). Furthermore each method of macrocyclisation should furnish product scaffolds containing different characteristic structural motifs. In the case of ring-closure by 1,3-dipolar cycloaddition, the resulting products **14** will contain a triazole ring system, a structural unit which is considered to act as a peptide bond mimic (both the *trans*- and the *cis*-amide bond configurations can be mimicked by the 1,4- and 1,5-triazoles, respectively).[14,29,36,37] Thus, such products can be considered to be macrocyclic peptidomimetics, a sub-class of macrocycles which is of considerable interest in drug discovery and which has attracted significant attention in recent years.[14,38] Macrocyclisation by ring-closing and ene-yne metathesis would furnish products containing synthetically versatile functional motifs (alkene and diene units, respectively) that could potentially serve as synthetic handles for further derivitisation around the macrocyclic cores. General structural type **15** is non-peptidic, a sub-class of macrocyles which is comparatively less-well explored in drug discovery.[10]

## 2.2. Proof of concept work

In order to establish the validity of the DOS strategy, the synthesis of a representative member of each of the three different general macrocyclic structural types **14**–**16** was targeted. We specifically chose compounds **19**–**21**, which we envisaged could be generated from building blocks **22**–**29** and **9** (Scheme 2).

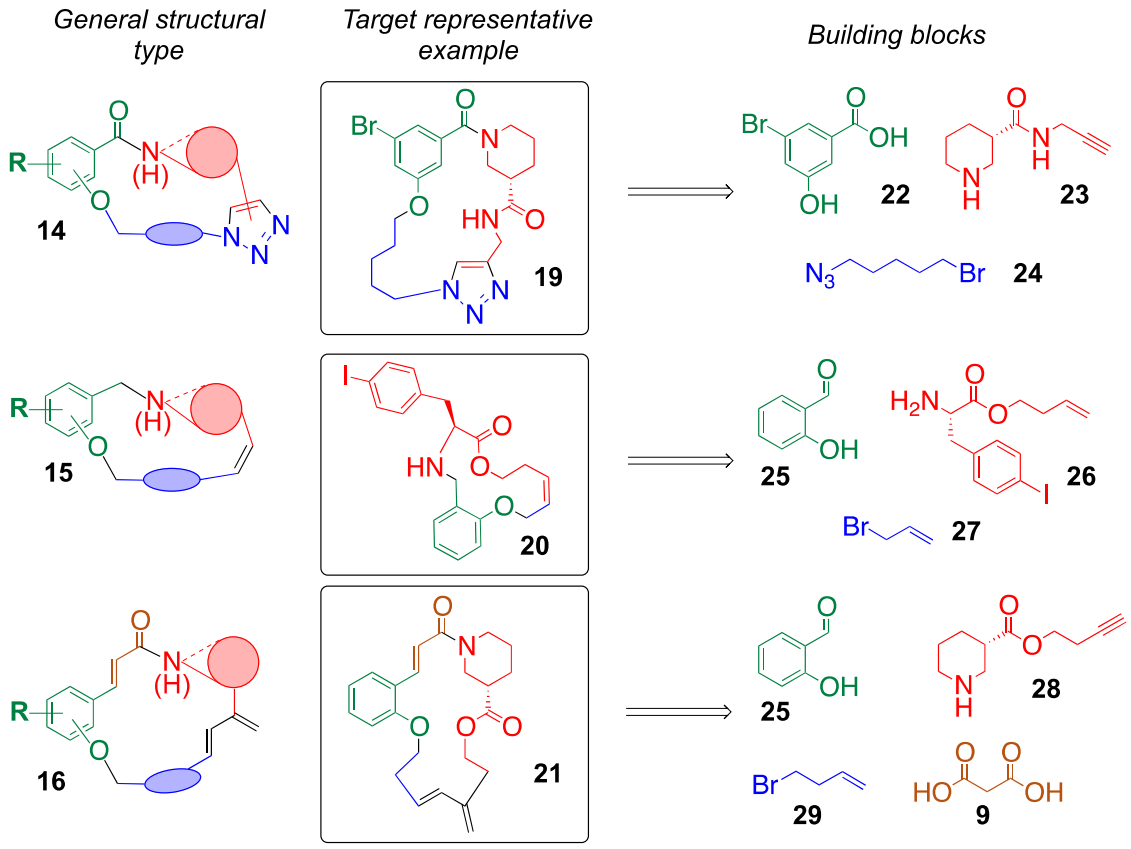
In addition to demonstrating the feasibility of the DOS, these specific compounds were selected as targets in order to probe both the synthetic versatility of the DOS and also its' capacity to furnish macrocyles with certain interesting or desirable structural characteristics. The target compounds covered a range of macrocyclic ring sizes and included both cyclic and acyclic amine motifs, as well as other functionalities and potential biomolecular interacting elements (e.g., hydrogen bond donors and acceptors). Each target macrocycle also included a chiral centre, which we assumed could be introduced through the use of chiral 'carbonyl capping' building blocks (**23**, **26** and **28**). If successful, this would demonstrate another method to introduce stereochemical diversity into the macrocycles through the building blocks (in addition to variation in the scaffold-defining elements), which should facilitate the probing of three-dimensional chemical space around the ring architectures. Target compounds **19** and **20** contained aryl halide motifs, which could potentially be further functionalised via various metal-catalysed cross-coupling processes. Successful synthesis of **19** would thus demonstrate that a functional group handle for derivitisation around the macrocyclic core could be introduced into compounds of the general form **14**. In the case of the representative example of macrocyles of the general form **20**, it was thought that it would be interesting to examine whether an additional synthetic handle for post-cyclisation structural elaboration could be installed which was orthogonal to the alkene unit introduced during macrocyclisation.

*2.2.1. Building block synthesis.* Building blocks **9**, **22**, **25**, **27** and **29** could be obtained from commercial sources. Amino-alkyne building block **23** was readily accessed from commercially available pyridine-acid **29** in three steps (Scheme 3). Amine protection generated the *N*-Boc derivative **30**. Propyl phosphonic acid anhydride (T3P) mediated coupling with alkynyl amine **31** furnished compound **32** and subsequent removal of the Boc group under acidic conditions yielded the desired building block **23** (isolated as the HCl-salt). Building block **28** could also be accessed (again as the corresponding HCl-salt) from **30** by EDC-mediated coupling with alkynyl alcohol **33** to form **34** followed by Boc deprotection. The synthesis of acyclic amino-alkene **26** was similarly straightforward. EDC-mediated coupling of commercially available carboxylic acid **35** and alkenyl alcohol **36** proceeded smoothly to generate ester **37** and subsequent acid-mediated Boc group removal afforded the target building block **26** (isolated as the HCl-salt). It was envisaged that azido-bromo 'hydroxyl capping' building block **24** could be generated in situ from the corresponding tosylate derivative **38** when required (see Section 2.2.2) which in turn was readily obtained from alcohol **39**.

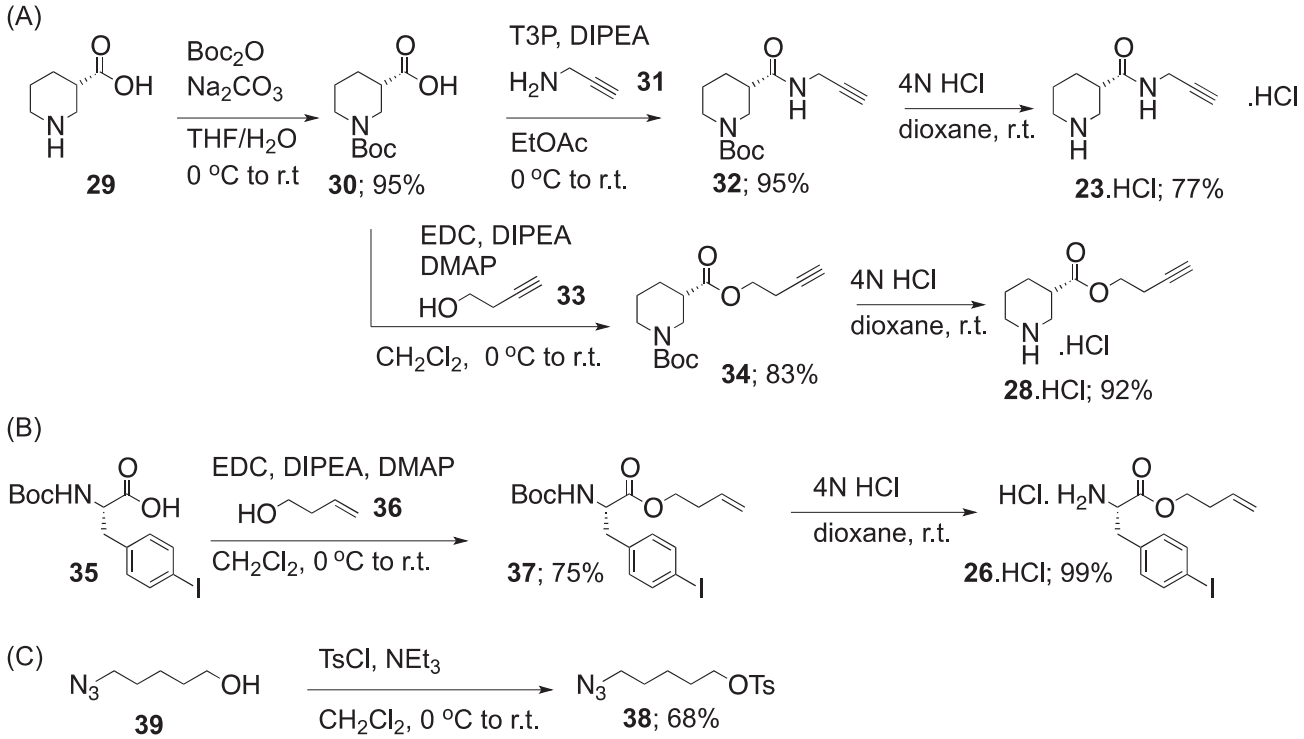
*2.2.2. Synthesis of target compound **19**.* The synthesis of compound **19** commenced with the esterification of hydroxy benzoic acid 'platform' building block **22** to generate compound **40** (Scheme 4). Coupling with 'hydroxyl capping' building block **24** (which was formed in situ from **38**), proceeded smoothly to afford compound **41**. Subsequent saponification of the ester moiety under basic conditions provided derivative **42**.[39] Coupling with amine 'carbonyl capping' building block **23** provided linear cyclization precursor **43** in a good yield. Pleasingly, 1,3-dipolar cycloaddition with copper catalysis proceeded smoothly and with a high degree of regioselectivity to furnish target macrocycle derivative **19** in a good yield.[40] The cycloaddition of **43** under ruthenium catalysis was investigated in an attempt to generate the regioisomeric macrocycle containing the 1,5-disubstituted triazole ring system. Although there was evidence for the formation of the desired product, it could not be isolated. Attention then turned towards the use of the alternative 'carbonyl capping' building block **44** in the DOS of compounds of the form **14**. Compound **44** was readily prepared from L-proline by an analogous route to the preparation of **23** (see Experimental Section). Coupling of **42** with **44** afforded acyclic precursor **45** in a high yield. Pleasingly, subsequent macrocyclisation under copper-catalysis again proceeded smoothly to furnish compound **46**, another macrocycle of the general form **14**.

*2.2.3. Synthesis of target compounds **20** and **21** from salicylaldehyde **25**.* It was anticipated that target macrocyclic compounds **20** and **21** could both be accessed from salicylaldehyde **25** (Scheme 5).

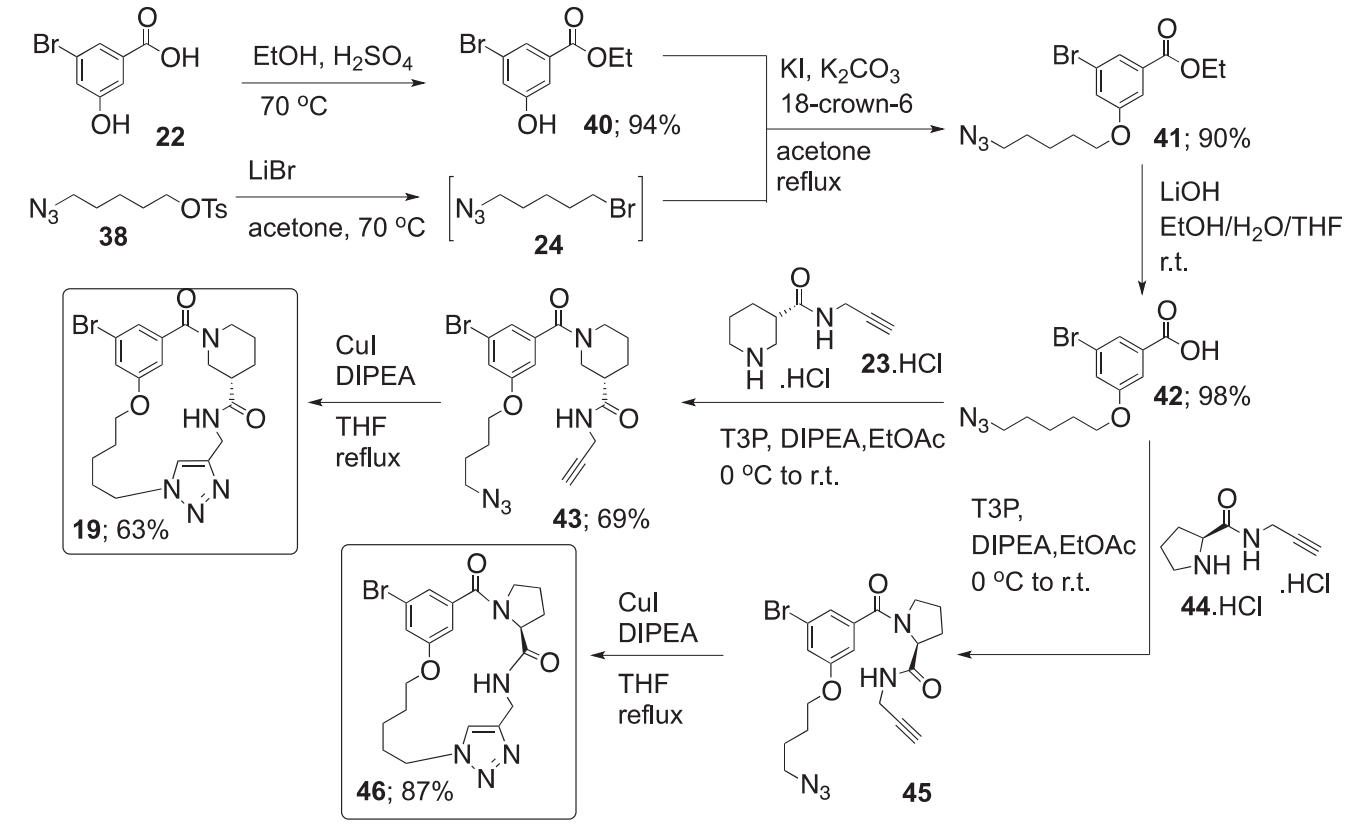
Attachment of the appropriate 'hydroxyl capping' building blocks **27** or **29** (*couple* stage) proceeded smoothly to furnish compounds **47** and **48**. Reductive amination of **47** with 'carbonyl capping' building block **26** furnished cyclization precursor **49**. In the *par* stage of the synthesis, the ring-closing metathesis of **49** with Hoveyda-Grubbs second generation catalyst was attempted, but no product formation was observed. It was thought that the lack of reactivity might be the result of deactivation of the metathesis catalyst via coordination to the free amine of substrate **49**. Thus, metathesis was attempted with the addition of one equivalent of *p*-toluenesulfonic acid hydrate ($PTSA \cdot H_2O$) to the reaction mixture in order to protonate the amine in situ. Pleasingly, this




**Scheme 2.** Proof-of-concept target macrocycles **19**–**21**.

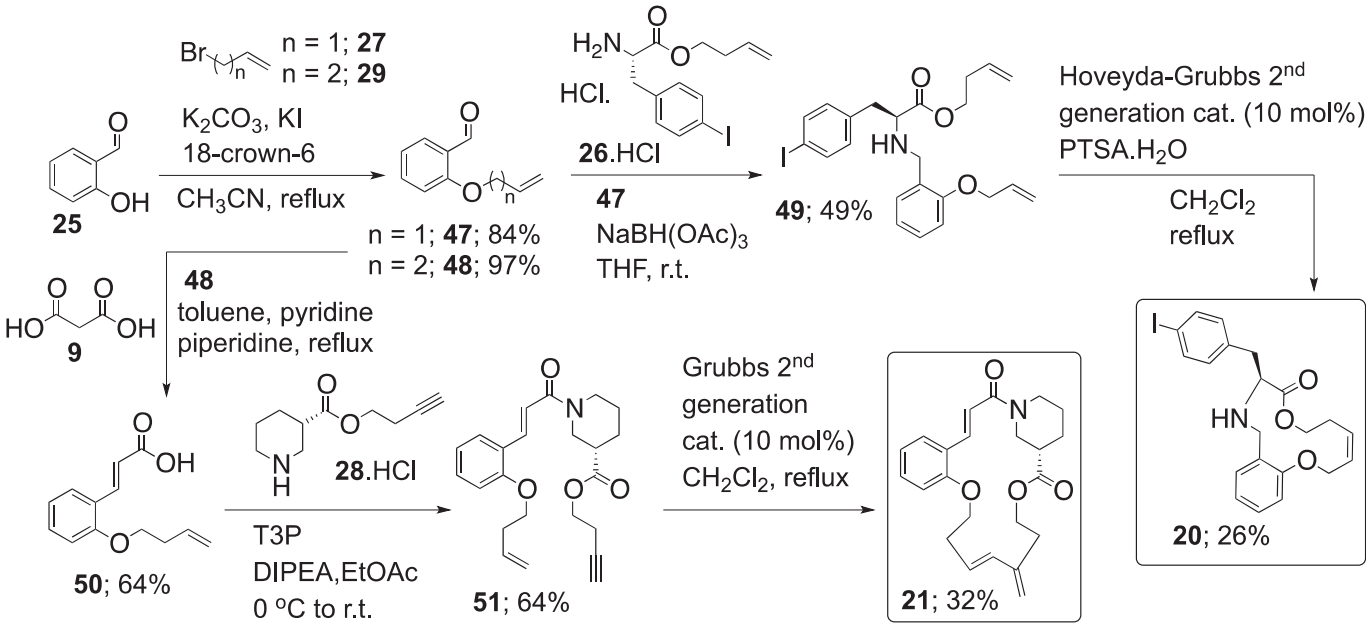



**Scheme 3.** Synthesis of building blocks.




**Scheme 4.** Synthesis of macrocycles **19** and **46**.

allowed access to target macrorycle **20**, albeit in a low yield (which was attributed to incomplete consumption of the starting material, despite the prolonged reaction time). Knoevenagel condensation of **48** with 'spacer' building block **9** (the second *couple* stage) afforded compound **50** and subsequent coupling with 'carbonyl capping' building block **28** (the third *couple* stage) led to the formation of macrocyclisation precursor **51**. In the *pair* stage of the synthesis, intramolecular ene-yne metathesis successfully afforded target




**Scheme 5.** Synthesis of macrocycles **20** and **21**.

compound **21**. The isolated yield of **21** was relatively low, which again could be attributed to incomplete consumption of starting material.

## 3. Conclusions

Herein, we have described a new strategy for the expedient DOS of novel and structurally diverse macrocyclic compounds which are based around a variety of distinct molecular scaffolds. The synthetic approach is based around the use of aromatic starting materials that bear an electrophilic carbonyl group and a nucleophilic hydroxyl group. These are designed to serve as 'platforms' onto which different building blocks can be attached to afford a range of distinct acyclic precursors. Subsequent intramolecular cyclisation reactions would then furnish different macrocyclic compounds. It was anticipated that the new DOS strategy would allow access to macrocyclic compounds of the general structural forms **14**–**16**. In a proof-of-concept study, the synthesis of four different novel macrocyclic compounds **19**–**21** and **46**, including representative examples of each of the different macrocyclic structural forms, was achieved. Each of these four previously unreported compounds was based around a distinct macrocyclic scaffold and contains functional motifs that could potentially interact with biological targets. These compounds are of significant interest from both a biological and synthetic perspective and their successful generation provides a validation of our new DOS strategy for the synthesis of structurally diverse macrocycles. We anticipate that this approach holds significant potential for library generation. It is step-efficient, proceeds from readily available starting materials and is modular in nature, which should allow for concise access to a diverse range of molecular scaffolds through variation in the building blocks attached to the core aromatic unit. The DOS strategy also features the use of three different macrocyclisation techniques, which allows for potential access to different structural motifs embedded within the macrocyclic architectures. Thus, we believe that this new DOS strategy represents a valuable contribution to the repertoire of strategies available for the synthesis of the biologically interesting macrocycle compound class. Larger library synthesis endeavours using this DOS algorithm are on-going. These, and the results of subsequent biological screening studies (which we hope will lead to the identification of novel antibacterial agents), will be reported in due course.

## 4. Experimental section

### 4.1. General information

All reagents and solvents were purchased from commercial sources and used without further purification unless otherwise stated. All the experiments were carried out under a nitrogen atmosphere unless otherwise stated. Melting points were measured using a Büchi B545 melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on precoated Merck silica gel $GF_{254}$ plates. IR spectra were recorded on a Perkin–Elmer Spectrum One (FT-IR) spectrophotometer. Flash column chromatography was performed on silica gel (230–400 mesh). $^1$H NMR and $^{13}$C NMR were recorded on a Bruker Avance 500 MHz instrument in $CDCl_3$, $(CD_3)_2CO$ and DMSO-$d_6$. HRMS was recorded on a Micromass Q-TOF mass spectrometer or a Waters LCT Premier Time of Flight mass spectrometer.

### 4.2. Experimental details and characterization data

*4.2.1. Synthesis of (S)-1-Boc-piperidine-3-carboxylic acid **(30)**.* (*S*)-Piperine-3-carboxylic acid **(29)** (4.00 g, 30.76 mmol) was dissolved in THF (230 mL) and $H_2O$ (230 mL). $Na_2CO_3$ (12.0 g, 113 mmol) was added at rt and the solution cooled to 0 °C. Boc-anhydride (7.38 g, 33.8 mmol) was added and the solution stirred at 0 °C for 2 h and then at rt for 12 h. The THF was removed under reduced pressure and resulting aqueous solution acidified with 10% HCl to pH 4. The aqueous layer was extracted with EtOAc (3×100 mL). The organic extracts were combined, washed with brine (80 mL) and dried ($Na_2SO_4$). The solvent was removed under reduced pressure to yield the title compound as a white solid (6.14 g, 87%). $[\alpha]_D^{20}$ +29.7 (*c* 1.0, $CHCl_3$). IR $\nu_{max}$ (neat)/cm$^{-1}$: 3167 w br (O–H str), 1730 s (C=O str), 1653 s (C=O str). $^1$H NMR (500 MHz, DMSO-$d_6$, 120 °C): $\delta$ 3.93 (1H, dd, *J* 12.9, 4.4 Hz, $-CH_2-$), 3.70 (1H, dt, *J* 12.9, 4.4 Hz, $-CH_2-$), 3.02 (1H, dd, *J* 12.9, 9.6 Hz, $-CH_2$), 2.94–2.87 (1H, m, $-CH_2-$), 2.37–2.31 (1H, m, –CH–), 1.97–1.91 (1H, m, $-CH_2-$), 1.70–1.55 (2H, m, $-CH_2-$), 1.46–1.35 (10H, m, $-CH_2-$ & $CH_3$). $^{13}$C NMR (125 MHz, DMSO-$d_6$, 120 °C): $\delta$ 174.5, 154.5, 79.2, 45.7, 44.0, 41.2, 28.6, 27.1, 24.2. HRMS (ESI$^+$) *m/z*=252.1212 $[M+Na]^+$ found, $C_{11}H_{19}O_4Na^+$ required 252.1206.

*4.2.2. Synthesis of (S)-1-Boc-(prop-2-yn-1-yl)piperidine-3-carboxamide **(32)**.* To a stirred solution of (*S*)-1-Boc-piperidine-3-carboxylic acid **(30)** (1.00 g, 4.36 mmol) in EtOAc (35 mL), propargylamine **(31)** (280 μL, 4.36 mmol) was added at rt and the resultant solution cooled to 0 °C. To this solution was added DIPEA (1.5 mL, 8.80 mmol) and a solution of 50 wt. % T3P in EtOAc (3.4 mL, 5.72 mmol). The solution was stirred for 30 min at 0 °C before being stirred at rt for 20 h. The reaction was quenched with $H_2O$ (5 mL) and the aqueous layer extracted with EtOAc (2×5 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent removed under reduced pressure to yield the title compound as a white solid (1.10 g, 95%). TLC $R_f$=0.12 (PE 30-40/EtOAc 7:3). IR $\nu_{max}$ (neat)/cm$^{-1}$: 3220 m (N–H str), 2967 m (C–H str), 2921 m (C–H str), 2860 m (C–H str), 1684 s (C=O str), 1631 s (C=O str). $^1$H NMR (500 MHz, $CD_3OD$): $\delta$ 4.07 (1H, br d, *J* 11.5 Hz, $-CH_2-$), 3.96 (1H, d, *J* 16.5 Hz, $-CH_2-$), 3.92 (2H, d, *J* 2.5 Hz, $-CH_2-$), 3.00–2.70 (2H, m, $-CH_2-$), 2.56 (1H, t, *J* 2.5 Hz, –CH), 2.33–2.27 (1H, m, –CH–), 1.92–1.88 (1H, m, $-CH_2-$), 1.72–1.62 (3H, m, $-CH_2-$), 1.44 (9H, s, $-CH_3$). $^{13}$C NMR (125 MHz, $CD_3OD$): $\delta$ 175.6, 156.4, 81.3, 80.6, 72.2, 45.7, 44.6, 44.1, 29.3, 28.9, 28.6, 25.5. HRMS (ESI$^+$) *m/z*=289.1536 $[M+Na]^+$ found, $C_{14}H_{22}O_3N_2Na^+$ required 289.1528.

*4.2.3. Synthesis of (S)-N-(prop-2-yn-1-yl)piperidine-3-carboxamide **(23)**.* (*S*)-1-Boc-(prop-$_2$–yn-1-yl)piperidine-3-carboxamide **(32)** (758 mg, 2.85 mmol) was dissolved in 4N HCl in 1,4-dioxane (26 mL) and stirred at rt for 2 h after which the solvent was removed under reduced pressure to yield the crude product as a brown solid. The crude product with triturated with chloroform to yield the title compound as a white salt (444 mg, 77%). IR $\nu_{max}$ (neat)/cm$^{-1}$: 3276 m (N–H str), 2931 w (C–H str), 1650 m (C=O str). $^1$H NMR (500 MHz, $CD_3OD$): $\delta$ 3.96 (2H, d, *J* 2.5 Hz, $-CH_2-$), 3.27–3.15 (3H, m, $-CH_2-$), 3.11–3.06 (1H, m, $-CH_2-$), 2.76–2.72 (1H, m, –CH–), 2.60 (1H, t, *J* 2.5 Hz, –CH), 2.02–1.89 (2H, m, $-CH_2-$), 1.82–1.73 (2H, m, $-CH_2-$). $^{13}$C NMR (125 MHz, $CD_3OD$): $\delta$ 174.2, 80.4, 72.3, 46.2, 45.1, 39.6, 29.4, 27.0, 21.2. HRMS (ESI$^+$) *m/z*=167.1180 $[M+H]^+$ found, $C_9H_{15}ON_2^+$ required 167.1179.

*4.2.4. Synthesis of 3-(but-3-yn-1-yl) (S)-1-Boc-piperidine-3-carboxylate **(34)**.* To a stirred solution of **30** (3.00 g, 13.1 mmol) in $CH_2Cl_2$ (30 mL), EDC (4.22 g, 22.0 mmol) was added at 0 °C with subsequent stirring for 40 min. To this solution was added DMAP (348 mg, 2.86 mmol), DIPEA (9.12 mL, 52.3 mmol) and 3-butyn-1-ol **(33)** (1.98 mL, 26.2 mmol). The solution was warmed to rt and stirred for 17 h. The solvent was removed under reduced pressure after which EtOAc (50 mL) was added. The organic phase was washed with 5% $NaHCO_3$ (2×50 mL), 5% citric acid (50 mL), $H_2O$ (30 mL) and then brine (30 mL). The organic extract was dried ($MgSO_4$) and the solvent removed under reduced pressure to yield

the title compound as an amorphous, off-white solid (3.04 g, 83%). TLC $R_f$=0.37 (Hexane/EtOAc 4:1). Mp 72–74 °C. $[\alpha]_D^{20}$ +28.1 ($c$=1.0, $CHCl_3$). IR $\nu_{max}$ (neat)/$cm^{-1}$: 3246 s (C–H str), 1726 s (C=O str), 1673 s (C=O str). $^1$H NMR (500 MHz, DMSO-$d_6$, 120 °C): $\delta$ 4.15 (2H, td, $J$ 6.6, 1.6 Hz, $-CH_2-$), 3.93 (1H, dd, $J$ 13.2, 4.1 Hz, $-CH_2-$), 3.68 (1H, dt, $J$ 13.2, 4.1 Hz, $-CH_2-$), 3.09 (1H, dd, $J$ 13.2, 9.5 Hz, $-CH_2-$), 2.98–2.92 (1H, m, $-CH_2-$), 2.59–2.43 (4H, m, $-CH_2-$, $-CH-$ & $-CH$), 1.99–1.91 (1H, m, $-CH_2-$), 1.72–1.61 (2H, m, $-CH_2-$), 1.47–1.37 (10H, m, $-CH_2-$ & $-CH_3$). $^{13}$C NMR (125 MHz, DMSO-$d_6$, 120 °C): $\delta$ 172.8, 154.5, 81.0, 79.2, 72.1, 62.4, 45.9, 44.0, 41.3, 28.6, 26.9, 24.1, 18.1. HRMS (ESI$^+$) $m/z$=304.1510 $[M+Na]^+$ found, $C_{15}H_{23}NO_4Na^+$ required 304.1519.

*4.2.5. Synthesis of but-3-yn-1-yl (S)-piperidine-3-carboxylate hydrochloride **(28)**.* **34** (140 mg, 498 μmol) was dissolved in 4N HCl in dioxane (3 mL) and stirred for 3 h, after which the solvent was removed under reduced pressure. To the residue was added $H_2O$ (7 mL) and the solution freeze dried to yield the title compound as a brown oil (100 mg, 92%). IR $\nu_{max}$ (neat)/$cm^{-1}$: 3282 w (N–H str), 2944 m (C–H str), 1726 s (C=O str). $^1$H NMR (500 MHz, DMSO-$d_6$, 120 °C): $\delta$ 9.53 (2H, br, -NH-), 4.22–4.15 (2H, m, $-CH_2-$), 3.34 (1H, dd, $J$ 12.3, 3.4 Hz, $-CH_2-$), 3.17 (1H, dt, $J$ 12.6, 3.8 Hz, $-CH_2-$), 2.97–2.92 (1H, m, $-CH_2-$), 2.87–2.82 (1H, m, $-CH_2-$), 2.67 (1H, t, $J$ 2.8 Hz, $-CH$), 2.54 (2H, td, $J$ 6.6, 2.8 Hz, $-CH_2-$), 2.08–2.01 (1H, m, $-CH_2-$), 1.91–1.79 (2H, m, $-CH_2-$), 1.69–1.60 (1H, m, $-CH_2-$). $^{13}$C NMR (125 MHz, DMSO-$d_6$, 120 °C): $\delta$=171.6, 81.0, 72.4, 62.8, 44.3, 43.3, 38.4, 25.1, 21.2, 18.6. HRMS (ESI$^+$) $m/z$=182.1183 $[M+H]^+$ found, $C_{10}H_{16}NO_2^+$ required 182.1181.

*4.2.6. Synthesis of but-3-en-1-yl Boc-4-iodo-L-phenylalanine **(37)**.* To a stirred solution of Boc-4-iodo-L-phenylalanine (2.00 g, 5.11 mmol) in $CH_2Cl_2$ (20 mL) was added EDC (2.34 g, 12.2 mmol), DMAP (183 mg, 1.50 mmol) and 3-buten-1-ol (1.20 mL) at 0 °C. The solution was warmed to rt and stirred for 19 h. The solution was diluted with $CH_2Cl_2$ (50 mL) and the organic phase washed with 5% $NaHCO_3$ (50 mL), $H_2O$ (30 mL) and then brine (30 mL). The organic extract was dried ($MgSO_4$) and the crude product purified by flash column chromatography eluting with 50% EtOAc in hexane to yield the title compound as crystalline, yellow solid (1.70 g, 75%). Mp=75–77 °C. TLC $R_f$=0.70 (Hexane/EtOAc 1:1). $[\alpha]_D^{20}$ +26.1 ($c$ 1.0, $CHCl_3$). IR $\nu_{max}$ (neat)/$cm^{-1}$: 3373 m (N–H str), 2972 m (C–H str), 1726 s (C=O str), 1687 s (C=O str), 1514 s (C=C str), 1485 m (C=C str), 1443 m (C=C str). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 7.62 (2H, d, $J$ 8.2 Hz, ArH), 7.27 (1H, t, $J$ 7.9 Hz, -NH-), 7.04 (2H, d, $J$ 8.2 Hz, ArH), 5.71 (1H, ddq, $J$ 17.4, 10.4, 6.7 Hz, $-CHCH_2$), 5.07 (1H, d, $J$ 17.1 Hz, $-CH_2$), 5.03 (1H, d, $J$ 10.4 Hz, $-CH_2$), 4.14–4.00 (3H, m, $-CH_2$ & $-CH$), 2.92 (1H, dd, $J$ 13.7, 5.5 Hz, $-CH_2-$), 2.79 (1H, dd, $J$ 13.7, 9.8 Hz, $-CH_2-$), 2.25 (2H, q, $J$ 7.3 Hz, $-CH_2-$), 1.31 (9H, s, $-CH_3$). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$=172.4, 155.8, 137.8, 137.4, 134.7, 132.0, 117.7, 92.7, 78.9, 64.0, 55.5, 36.4, 32.9, 28.5. HRMS (ESI$^+$) $m/z$=468.0637 $[M+Na]^+$ found, $C_{18}H_{24}NO_4^{127}INa^+$ required 468.0642.

*4.2.7. Synthesis of but-3-en-1-yl 4-iodo-L-phenylalanine hydrochloride **(26)**.* **37** (1.59 g, 3.57 mmol) was dissolved in 4N HCl in dioxane (24 mL) and stirred for 3 h, after which the solvent was removed under reduced pressure. To the residue was added $H_2O$ (25 mL) and the solution freeze dried to yield the title compound as a crystalline off-white solid (1.36 g, 100%). Mp 145–147 °C. $[\alpha]_D^{20}$ +17.3 ($c$ 1.0, $CHCl_3$). IR $\nu_{max}$ (neat)/$cm^{-1}$: 3147 w (N–H str), 2845 m (C–H str), 1738 s (C=O str), 1641 w (C=C str), 1606 w (C=C str). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 7.69 (2H, d, $J$ 8.2 Hz, ArH), 7.05 (2H, d, $J$ 8.5 Hz, ArH), 5.64 (1H, ddq, $J$ 17.0, 10.2, 6.5 Hz, $-CHCH_2$), 5.08–5.01 (2H, m, $-CH_2$), 4.23 (1H, dd, $J$ 7.5, 6.1 Hz, $-CH-$), 4.10 (2H, t, $J$ 6.1 Hz, $-CH_2-$), 3.10 (1H, dd, $J$ 14.0, 6.1 Hz, $-CH_2-$), 3.00 (1H, dd, $J$ 14.0, 7.5 Hz, $-CH_2-$), 2.24 (2H, q, $J$ 6.8 Hz, $-CH_2-$).$^{13}$C NMR (125 MHz, DMSO-$d_6$: $\delta$ 169.1, 137.7, 134.6, 134.3, 132.1, 117.8, 93.8, 65.1, 53.2, 35.7, 32.4). HRMS (ESI$^+$) $m/z$=346.0317 $[M+H]^+$ found, $C_{13}H_{17}NO_2^{127}I^+$ required 346.0304.

*4.2.8. Synthesis of 5-azidopentyl tosylate **(38)**.* To a stirred solution of 5-azidopentyl alcohol **(39)** (4.44 g, 34.3 mmol) in $CH_2Cl_2$ (213 mL) was added TEA (4.78 mL) and TsCl (9.82 g, 51.5 mmol) at 0 °C. The solution was allowed to warm to rt and stirred for 19 h. $CH_2Cl_2$ (100 mL) was added and the organic layer washed with $H_2O$ (2×100 mL) and brine (50 mL). The organic extract was dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product purified by flash column chromatography, eluting with a gradient from 5% to 20% EtOAc in hexane to yield the title compound as a colourless oil (6.59 g, 68%). TLC $R_f$=0.19 (Hexane/EtOAc 9:1). IR $\nu_{max}$ (neat)/$cm^{-1}$: 2937 m (C–H str), 2871 m (C–H str), 2091 s ($N_3$ str), 1596 m (C=C str), 1451 m (C=C str), 1350 s (S=O str), 1176 s (S=O str). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.77 (2H, d, $J$ 6.4 Hz, ArH), 7.33 (2H, d, $J$ 6.4 Hz, ArH), 4.01 (2H, t, $J$ 6.4 Hz, $-CH_2-$), 3.21 (2H, t, $J$=6.8 Hz, $-CH_2-$), 2.42 (3H, s, $-CH_3$), 1.69–1.62 (2H, m, $-CH_2-$), 1.56–1.48 (2H, m, $-CH_2-$), 1.41–1.34 (2H, m, $-CH_2-$). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 144.8, 132.9, 129.8, 127.8, 70.1, 51.0, 28.3, 28.1, 22.6, 21.6. HRMS (ESI$^+$) $m/z$=306.0895 $[M+Na]^+$ found, $C_{12}H_{17}O_3N_3SNa^+$ required 306.0883.

*4.2.9. Synthesis of ethyl 3-bromo-5-hydroxybenzoate **(40)**.* To a stirred solution of 3-bromo-5-hydroxy benzoic acid **(22)** (5.19 g, 23.9 mmol) in EtOH (50 mL), $H_2SO_4$ (1 mL) was added at rt and the solution refluxed at 70 °C for 72 h. The solvent was removed under reduced pressure and to it added EtOAc (100 mL). The organic phase was washed with satd $NaHCO_3$ (2×50 mL) and brine (50 mL). The organic extract was dried ($MgSO_4$) and the solvent removed under reduced pressure to yield the title compound as an orange solid (5.48 g, 94%). Mp 99–101 °C (lit. value 96 °C). TLC $R_f$=0.25 (PE 30-40/EtOAc 9:1). IR $\nu_{max}$ (neat)/$cm^{-1}$: 3392 m br (O–H str), 3094 w (C–H str), 2972 w (C–H str), 2926 w (C–H str), 1691 s (C=O str), 1603 m (C=C str), 1588 m (C=C str), 1480 m (C=C str), 1461 m (C=C str), 1439 m (C=C str). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.72 (1H, d, $J$ 1.2 Hz, ArH), 7.53 (1H, dd, $J$ 2.4, 1.2 Hz, ArH), 7.22 (1H, dd, $J$ 2.4, 2.0 Hz, ArH), 4.37 (2H, q, $J$ 7.2 Hz, $-CH_2-$), 1.38 (3H, t, $J$ 7.2 Hz, $-CH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 165.7, 156.6, 132.9, 124.8, 123.3, 122.8, 115.5, 61.8, 14.2. HRMS (ESI$^+$) $m/z$=266.9634 $[M+Na]^+$ found, $C_9H_9O_3BrNa^+$ required 266.9627.

These data are consistent with those previously reported.[41]

*4.2.10. Synthesis of ethyl 3-((5-azidopentyl)oxy)-5-bromobenzoate **(41)**.* A solution of **38** (4.65 g, 16.4 mmol) and LiBr (4.27 g, 49.2 mmol) in acetone (53 mL) was refluxed at 70 °C for 18 h. The solution was filtered to remove the precipitate yielding a solution of the corresponding bromide **24** in acetone (53 mL). Ethyl 3-bromo-5-hydroxybenzoate **(40)** (1.34 g, 5.47 mmol), KI (83 mg, 500 μmol), 18-crown-6 (66 mg, 250 μmol) and $K_2CO_3$ (2.27 g, 16.4 mmol) were added to the solution of **24** at rt. The mixture was refluxed at 70 °C for 42 h. The solvent was then removed under reduced pressure, EtOAc (60 mL) added and the organic layer washed with $H_2O$ (60 mL). The aqueous layer was separated and extracted with EtOAc (60 mL). The organic extracts were combined, washed with $H_2O$ (60 mL) and brine (30 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography, eluting with a gradient from 2% to 4% EtOAc in petroleum ether 30–40 to yield the title compound as an orange oil (1.94 g, 98%). TLC $R_f$=0.29 (Hexane/EtOAc 19:1). IR $\nu_{max}$ (neat)/$cm^{-1}$: 2932 m (C–H str), 2086 s ($N_3$ str), 1719 s (C=O str), 1593 m (C=C str), 1570 m (C=C str), 1439 m (C=C str), 1391 w (C=C str), 1360 w (C=C str). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.74 (1H, t, $J$ 1.5 Hz, ArH), 7.47 (1H, dd, $J$ 2.5, 1.5 Hz, ArH), 7.21 (1H, s, ArH), 4.35 (2H, q, $J$ 7.0 Hz, $-CH_2-$), 3.99 (2H, t, $J$ 6.0 Hz, $-CH_2-$), 3.31 (2H, t, $J$ 7.0 Hz, $-CH_2-$), 1.84–1.79 (2H, m, $-CH_2-$), 1.70–1.64 (2H, m,

–$CH_2$–), 1.59–1.52 (2H, m, –$CH_2$–), 1.38 (3H, t, *J* 7.0 Hz, –$CH_3$). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 165.6, 160.0, 133.5, 125.2, 123.0, 122.8, 114.4, 68.6, 61.9, 51.7, 29.0, 23.7, 14.7. HRMS (ESI$^+$) *m/z*=378.0430 $[M+Na]^+$ found, $C_{14}H_{18}O_3N_3BrNa^+$ required 378.0424.

*4.2.11. Synthesis of 3-((5-azidopentyl)oxy)-5-bromobenzoic acid **(42)**.* To a stirred solution of ethyl 3-((5-azidopentyl)oxy)-5-bromobenzoate **(41)** (1.57 g, 4.41 mmol) in EtOH (13.2 mL) and THF (4.4 mL) was added a solution of LiOH (231 mg, 5.50 mmol) in $H_2O$ (4.4 mL) at rt. The solution was stirred for 16 h and then acidified with 10% HCl to pH 3. The aqueous layer was extracted with EtOAc (2×80 mL) and the organic extracts were combined, washed with $H_2O$ (50 mL), brine (50 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield the title compound as an orange solid (1.30 g, 90%). Mp 102–104 °C. IR $\nu_{max}$ (neat)/cm$^{-1}$: 2942 w br (O–H str), 2081 s ($N_3$ str), 1686 s (C=O str), 1590 m (C=C str), 1573 m (C=C str), 1461 m (C=C str), 1432 m (C=C str), 1418 m (C=C str), 1398 m (C=C str). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.81 (1H, t, *J* 1.6 Hz, ArH), 7.53–7.51 (1H, m, ArH), 7.27 (1H, dd, *J* 1.8, 1.6 Hz, ArH), 4.00 (2H, t, *J* 6.2 Hz, –$CH_2$–), 3.30 (2H, t, *J* 6.4 Hz, –$CH_2$–), 1.87–1.80 (2H, m, –$CH_2$–), 1.71–1.63 (2H, m, –$CH_2$–), 1.61–1.57 (2H, m, –$CH_2$–). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 169.3, 159.7, 131.5, 125.4, 123.4, 122.8, 114.5, 68.2, 51.3, 28.6, 23.3. HRMS (ESI$^+$) *m/z*=350.0112 $[M+Na]^+$ found, $C_{12}H_{14}O_3N_3BrNa^+$ required 350.0111.

*4.2.12. Synthesis of azido-alkyne **(43)**.* (*S*)-*N*-(prop-2-yn-1-yl)piperidine-3-carboxamide **(23)** (31 mg, 150 μmol) and 3-((5-azidopentyl)oxy)-5-bromobenzoic acid **(42)** (50 mg, 150 μmol) were dissolved in EtOAc (1.2 mL) at rt and then cooled to 0 °C. To this solution was added DIPEA (100 μL, 600 μmol) and a solution of 50 wt. % T3P in EtOAc (120 μL, 195 μmol). The solution was stirred at 0 °C for 30 min before being stirred at rt for 20 h. The reaction was quenched with $H_2O$ (20 mL) and EtOAc (20 mL) was added. The organic layer was separated and washed with 5% citric acid (2×20 mL), 5% $NaHCO_3$ (20 mL) and then brine (20 mL). The organic extract was dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was purified with flash column chromatography, eluting with 60% EtOAc in petroleum ether 30–40 to yield the title compound as a colourless oil (49 mg, 69%). TLC $R_f$=0.25 (PE 30-40/EtOAc 4:6). IR $\nu_{max}$ (neat)/cm$^{-1}$: 2937 w (C–H str), 2865 w (C–H str), 2096 s ($N_3$ str), 1623 m (C=O str), 1563 m (C=C str), 1464 m (C=C str), 1434 m (C=C str). $^1$H NMR (500 MHz, DMSO-$d_6$): δ 7.26 (1H, s, ArH), 7.02 (1H, s, ArH), 6.73 (1H, s, ArH), 4.57–4.14 (1H, m, –$CH_2$–), 4.06 (2H, t, *J* 7.0 Hz, –$CH_2$–), 3.93 (2H, s, –$CH_2$–), 3.64–3.57 (1H, m, –$CH_2$–), 3.34 (2H, t, *J* 7.0 Hz, –$CH_2$–), 3.18–3.03 (2H, m, –$CH_2$–), 2.55–2.36 (2H, m, –CH– & –CH), 2.00–1.72 (4H, m, –$CH_2$–), 1.61–1.21 (6H, m, –$CH_2$–). $^{13}$C NMR (125 MHz, DMSO-$d_6$)–Exists as a mixture of rotamers: δ 174.1, 170.6, 161.5, 139.8, 124.0, 122.6, 120.1, 113.0, 80.5, 72.2, 69.5, 52.4, 50.8, 45.6, 44.1, 43.6, 29.7, 29.4, 28.7, 26.1, 25.0. HRMS (ESI$^+$) *m/z*=476.1313 $[M+H]^+$ found, $C_{21}H_{27}O_3N_5Br^+$ required 476.1297.

*4.2.13. Synthesis of macrocycle **(19)**.* To a solution of **43** (17 mg, 36.0 μmol) in THF (20 mL) was added CuI (13.6 mg, 71.0 μmol) and DIPEA (18 μL, 107 μmol) at rt. The solution was refluxed at 70 °C for 44 h. The solvent was removed under reduced pressure and the crude product purified by flash column chromatography, eluting with 5% MeOH in EtOAc to yield the title compound as a colourless oil (14.3 mg, 30.0 μmol, 83%). TLC $R_f$=0.15 (EtOAc/MeOH 19:1). IR $\nu_{max}$ (neat)/cm$^{-1}$: 2942 w (C–H str), 2865 w (C–H str), 1661 m (C=O str), 1630 m (C=O str), 1603 m (C=C str), 1560 m (C=C str), 1467 m (C=C str), 1449 m (C=C str), 1436 m (C=C str). $^1$H NMR (400 MHz, $CD_3OD$): δ 7.80 (1H, s, –CH–), 7.15 (1H, t, *J* 2.0 Hz, ArH), 7.09 (1H, s, ArH), 6.78 (1H, s, ArH), 4.78 (1H, d, *J* 14.8 Hz, –$CH_2$–), 4.57–4.32 (3H, m, –$CH_2$–), 4.04–3.92 (3H, m, –$CH_2$–), 3.72 (1H, d, *J* 13.6 Hz, –$CH_2$–), 3.13 (1H, dd, *J* 13.6, 10.0 Hz, –$CH_2$–), 2.88–2.81 (1H, m, –$CH_2$–), 2.47–2.42 (1H, m, –CH–), 2.13–1.53 (6H, m, –$CH_2$–), 1.52–1.47 (2H, m, –$CH_2$–), 1.38–1.12 (2H, m, –CH2-). $^{13}$C NMR (100 MHz, $CD_3OD$): δ 173.4, 168.4, 159.1, 137.8, 123.3, 122.3, 116.2, 112.8, 67.3, 50.1, 49.5, 43.5, 42.2, 33.5, 29.1, 28.2, 27.9, 24.0, 23.1. HRMS (ESI$^+$) *m/z*=476.1306 $[M+H]^+$ found, $C_{21}H_{27}O_3N_5Br^+$ required 476.1292.

*4.2.14. Synthesis of (S)-N-(prop-2-yn-1-yl)proline carboxamide hydrochloride **(44)**.* To a stirred solution of L-proline (5.00 g, 43.4 mmol) in THF (325 mL) and $H_2O$ (325 mL), $Na_2CO_3$ (17.3 g, 162 mmol) was added at rt and the resultant solution cooled to 0 °C. Following the addition of Boc-anhydride (10.4 g, 47.8 mmol), the solution was stirred at 0 °C for 2 h and then at rt for 18 h. The THF was removed under reduced pressure and the resulting aqueous solution acidified with 1M HCl to pH 4. The aqueous layer was extracted with EtOAc (3×50 mL) and the organic extracts were combined and dried ($Na_2SO_4$). The solvent was removed under reduced pressure to yield *N*-Boc-L-proline. To a stirred solution of *N*-Boc-L-proline (2.00 g, 9.29 mmol) in EtOAc (70 mL), propargylamine **(31)** (600 μL, 9.34 mmol) was added at rt and then cooled to 0 °C. To this solution was added DIPEA (3.2 mL, 18.8 mmol) and a solution of 50 wt. % T3P in EtOAc (7.25 mL, 12.2 mmol). The solution was stirred at 0 °C for 30 min before being stirred at rt for 20 h. The reaction was quenched with $H_2O$ (50 mL), EtOAc (50 mL) was added and the organic layer separated and washed with 5% $NaHCO_3$ (50 mL), 5% citric acid (50 mL) and brine (50 mL). The organic extract was dried ($MgSO_4$) and the solvent removed under reduced pressure to yield (*S*)-1-Boc-(prop-2-yn-1-yl)proline carboxamide. (*S*)-1-Boc-(prop-2-yn-1-yl)proline carboxamide (734 mg, 2.80 mmol) was dissolved in 4N HCl in 1,4-dioxane (26 mL) and stirred at rt for 2 h after which the solvent was removed under reduced pressure to yield the crude product as a brown solid. The crude product with triturated with chloroform to yield the title compound as a white salt (470 mg, 47% over three steps). IR $\nu_{max}$ (neat)/cm$^{-1}$: 3235 m (N–H str), 2911 m (C–H str), 1687 m (C=O str). $^1$H NMR (400 MHz, $CD_3OD$): δ 4.14 (1H, t, *J* 7.6 Hz, –CH–), 3.93 (2H, d, *J* 2.4 Hz, –$CH_2$–), 3.31–3.22 (2H, m, –$CH_2$–), 2.56 (1H, t, *J* 2.4 Hz, –CH), 2.35–2.30 (1H, m, –$CH_2$–), 1.97–1.87 (3H, m, –$CH_2$–). $^{13}$C NMR (100 MHz, $CD_3OD$): δ 169.2, 79.9, 72.8, 61.1, 47.3, 30.8, 29.8, 25.0. HRMS (ESI$^+$) *m/z*=153.1021 $[M+H]^+$ found, $C_8H_{13}ON_2^+$ required 153.1022.

*4.2.15. Synthesis of azido-alkyne **(45)**.* (*S*)-*N*-(prop-2-yn-1-yl)proline carboxamide hydrochloride **(44)** (28 mg, 150 μmol) and 3-((5-azidopentyl)oxy)-5-bromobenzoic acid **(42)** (50 mg, 150 μmol) were dissolved in EtOAc (1.2 mL) at rt and then cooled to 0 °C. To this solution was added DIPEA (100 μL, 600 μmol) and a solution of 50 wt. % T3P in EtOAc (120 μL, 195 μmol). The solution was stirred at 0 °C for 30 min before being stirred at rt for 20 h. The reaction was quenched with $H_2O$ (20 mL) and EtOAc (20 mL) was added. The organic layer was separated and washed with 5% citric acid (2×20 mL), 5% $NaHCO_3$ (20 mL) and then brine (20 mL). The organic extract was dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was purified with flash column chromatography, eluting with 60% EtOAc in petroleum ether 30–40 to yield the title compound as a colourless oil (65 mg, 93%). TLC $R_f$=0.25 (PE 30-40/EtOAc 4:6). IR $\nu_{max}$ (neat)/cm$^{-1}$: 3291 m (N–H str), 2937 w (C–H str), 2876 w (C–H str), 2096 s ($N_3$ str), 1661 m (C=O str), 1621 m (C=O str), 1568 m (C=C str), 1454 m (C=C str), 1431 m (C=C str), 1413 m (C=C str). $^1$H NMR (500 MHz, DMSO-$d_6$, 120 °C): δ 7.20 (1H, s, ArH), 7.10 (1H, s, ArH), 6.68 (1H, s, ArH), 4.41

(1H, br, –CH–), 4.06 (2H, m, $-CH_2-$), 3.95–3.82 (2H, m, $-CH_2-$), 3.58–3.46 (2H, m, $-CH_2-$), 3.34 (2H, t, *J* 6.8 Hz, $-CH_2-$), 2.79 (1H, t, *J* 2.5 Hz, –CH), 2.20–2.16 (1H, m, $-CH_2-$), 1.94–1.83 (3H, m, $-CH_2-$), 1.81–1.75 (2H, m, $-CH_2-$), 1.69–1.62 (2H, m, $-CH_2-$), 1.57–1.52 (2H, m, $-CH_2-$). $^{13}$C NMR (125 MHz, DMSO-$d_6$, 120 °C): δ 171.8, 167.6, 159.7, 140.3, 122.4, 122.3, 118.9, 113.1, 81.4, 73.5, 68.4, 61.2, 51.0, 47.2, 30.1, 28.5, 25.4, 23.2. HRMS (ESI$^+$) *m/z*=462.1137 $[M+H]^+$ found, $C_{20}H_{25}O_3N_5Br^+$ required 462.1135.

*4.2.16. Synthesis of macrocycle **(46)**.* To a solution of **45** (40.0 mg, 87.0 μmol) in THF (40 mL) was added CuI (28.4 mg, 150 μmol) and DIPEA (42.0 μL, 240 μmol) at rt. The solution was refluxed at 70 °C for 20 h. The solvent was removed under reduced pressure and the crude product purified by flash column chromatography, eluting with 5% MeOH in EtOAc to yield the title compound as a colourless oil (34.7 mg, 87%). TLC $R_f$=0.15 (EtOAc/MeOH 19:1). IR $\nu_{max}$ (neat)/cm$^{-1}$: 2932 w (C–H str), 2876 w (C–H str), 1618 m (C=O str), 1601 m (C=C str), 1560 m (C=C str), 1451 m (C=C str), 1436 m (C=C str), 1413 m (C=C str). $^1$H NMR (400 MHz, $CD_3OD$): δ 7.76 (1H, s, –CH–), 7.16 (1H, s, ArH), 7.13 (1H, s, ArH), 6.67 (1H, s, ArH), 4.57 (1H, d, *J* 15.2 Hz, $-CH_2-$), 4.44–4.50 (2H, m, $-CH_2-$), 4.29–4.23 (2H, m, $-CH_2-$ & –CH–), 3.90–3.88 (2H, m, $-CH_2-$), 3.78–3.67 (2H, m, $-CH_2-$), 2.22–1.94 (6H, m, $-CH_2-$), 1.81–1.75 (2H, m, $-CH_2-$), 1.42–1.25 (2H, m, $-CH_2-$). $^{13}$C NMR (100 MHz, $CD_3OD$): δ 174.3, 170.1, 160.8, 146.2, 140.4, 124.6, 124.4, 123.0, 117.7, 114.5, 68.3, 64.4, 50.4, 47.9, 35.8, 33.1, 29.1, 27.8, 23.2, 22.4. HRMS (ESI$^+$) *m/z*=462.1145 $[M+H]^+$ found, $C_{20}H_{25}O_3N_5Br^+$ required 462.1135.

*4.2.17. Synthesis of 2-(allyloxy)benzaldehyde **(47)**.* To a stirred solution of salicylaldehyde (20.0 g, 164 mmol) in acetonitrile (200 mL) was added allylbromide **(27)** (29.0 mL, 333 mmol), KI (544 mg, 3.28 mmol), 18-crown-6 (432 mg, 1.64 mmol) and $K_2CO_3$ (66.0 g, 478 mmol) at rt after which the solution was refluxed at 75 °C for 18 h. The $K_2CO_3$ was filtered off and the solvent removed under reduced pressure. $H_2O$ (100 mL) was added and the aqueous layer extracted with EtOAc (2×100 mL). The organic layers were combined, washed with brine (50 mL), dried ($Na_2SO_4$) and the solvent removed under reduced pressure to yield the title compound as an orange oil (24.2 g, 84%). TLC $R_f$=0.28 (Hexane/EtOAc 19:1). IR $\nu_{max}$ (neat)/cm$^{-1}$: 2861 w (C–H str), 1681 s (C=O str), 1598 s (C=C str), 1483 m (C=C str), 1457 m (C=C str). $^1$H NMR (400 MHz, $CDCl_3$): δ 10.51 (1H, s, –CHO), 7.80 (2H, dd, *J* 7.5, 1.7 Hz, ArH), 7.50 (1H, ddd, *J* 8.5, 7.5, 2.0 Hz, ArH), 6.99 (1H, t, *J* 7.5 Hz, ArH), 6.95 (1H, d, *J* 8.5 Hz, ArH), 6.10–6.00 (1H, m, $-CHCH_2$), 5.43 (1H, dq, *J* 17.4, 1.7 Hz, $-CH_2$), 5.31 (1H, dq, *J* 10.6, 1.4 Hz, $-CH_2$), 4.63 (1H, dt, *J*=5.1, 1.4 Hz, $-CH_2-$). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 189.7, 160.9, 135.9, 132.4, 128.4, 125.1, 120.9, 118.1, 112.9, 69.2. HRMS (ESI$^+$) *m/z*=163.0751 $[M+H]^+$ found, $C_{10}H_{11}O_2^+$ required 163.0754.

*4.2.18. Synthesis of 2-(but-3-en-1-yloxy)benzaldehyde **(48)**.* To a stirred solution of salicylaldehyde (1.00 g, 8.19 mmol) in acetonitrile (10 mL) was added 4-bromobut-1-ene **(29)** (2.90 mL, 16.2 mmol), KI (136 mg, 819 μmol), 18-crown-6 (108 mg, 409 μmol) and $K_2CO_3$ (3.30 g, 23.9 mmol) at rt after which the solution was refluxed at 75 °C for 18 h. The solvent was removed under reduced pressure, $H_2O$ (50 mL) was added and the aqueous layer extracted with EtOAc (2×50 mL). The organic layers were combined, washed with brine (50 mL), dried ($Na_2SO_4$) and the solvent removed under reduced pressure to yield the title compound as a yellow oil (1.40 g, 97%). TLC $R_f$=0.25 (Hexane/EtOAc; 19:1). IR $\nu_{max}$ (neat)/cm$^{-1}$: 2936 w (C–H str), 1685 s (C=O str), 1600 s (C=C str), 1485 s (C=C str), 1459 s (C=C str).$^1$H NMR (400 MHz, $CDCl_3$): δ 10.49 (1H, s, –CHO), 7.82 (1H, dd, *J* 7.7, 1.8 Hz, ArH), 7.52 (1H, dt, *J* 7.2, 1.8 Hz, ArH), 7.01 (1H, t, *J* 7.8 Hz, ArH), 6.96 (1H, d, *J* 8.4 Hz, ArH), 5.89 (1H, ddt, *J* 17.1, 10.3, 6.8 Hz, $-CHCH_2$), 5.18 (1H, dq, *J* 17.1, 1.6 Hz, $-CHCH_2$), 5.12 (1H, dq, *J* 10.2, 1.7 Hz, $-CHCH_2$), 4.13 (2H, t, *J* 6.5 Hz, $-CH_2-$), 2.60 (2H, tq, *J* 6.6, 1.4 Hz, $-CH_2-$). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 189.9, 161.3, 135.9, 134.0, 128.2, 125.0, 120.7, 117.6, 112.5, 67.7, 33.5. HRMS (ESI$^+$): *m/z*=199.0723 $[M+Na]^+$ found, $C_{11}H_{12}O_2Na^+$ required 199.0730.

*4.2.19. Synthesis of but-3-en-1-yl (S)-2-((2-(allyloxy)benzyl)amino)-3-(4-iodophenyl)propanoate **(49)**.* To a stirred solution of **47** (50 mg, 308 μmol) and **26** (130 mg, 341 μmol) in THF (3 mL) was added $NaBH(OAc)_3$ (290 mg, 1.37 mmol) at rt, after which the solution was stirred for 18 h. The reaction was quenched with 1M NaOH (10 mL) and extracted with EtOAc (3×20 mL). The organic layers were combined and washed with brine (20 mL). The organic extract was dried ($MgSO_4$) and the crude product purified by flash column chromatography, eluting with a gradient from 10% to 15% EtOAc in petroleum ether 30–40 to yield the title compound as a pale yellow oil (73.5 mg, 49%). TLC $R_f$=0.47 (PE 30-40/EtOAc 7:3). $[\alpha]_D^{20}$ +6.6 (*c* 1.0, $CHCl_3$). IR $\nu_{max}$ (neat)/cm$^{-1}$: 2960 w (C–H str), 2861 w (C–H str), 1728 s (C=O str), 1643 w (C=C str), 1602 w (C=C str), 1588 w (C=C str). $^1$H NMR (500 MHz, $CDCl_3$): δ 7.55 (2H, d, *J* 8.5 Hz, ArH), 7.19 (1H, td, *J* 7.6, 1.8 Hz, ArH), 7.13 (1H, dd, *J* 7.3, 1.8 Hz, ArH), 6.89–6.86 (3H, m, ArH), 6.77 (1H, d, *J* 7.6 Hz, ArH), 5.95 (1H, ddt, *J* 17.4, 10.4, 4.9 Hz, $-CHCH_2$), 5.68 (1H, ddt, *J* 17.1, 10.4, 6.7 Hz, $-CHCH_2$), 5.35 (1H, dq, *J* 17.1, 1.5 Hz, $-CH_2$), 5.24 (1H, dq, *J* 10.7, 1.5 Hz, $-CH_2$), 5.09–5.04 (2H, m, $-CH_2$), 4.48–4.38 (2H, m, $-CH_2-$), 4.06 (2H, t, *J* 6.7 Hz, $-CH_2-$), 3.85 (1H, d, *J* 13.4 Hz, $-CH_2-$), 3.65 (1H, d, *J* 13.4 Hz, $-CH_2-$), 3.47 (1H, dd, *J* 7.6, 6.1 Hz, –CH–), 2.90 (1H, dd, *J* 13.7, 6.1 Hz, $-CH_2-$), 2.83 (1H, dd, *J* 13.7, 7.6 Hz, $-CH_2-$), 2.30 (2H, qdd, *J* 6.7, 1.5, 1.2 Hz, $-CH_2-$). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 174.1, 156.6, 137.4, 137.1, 133.8, 133.2, 131.2, 129.9, 128.3, 127.7, 120.5, 117.3, 117.0, 111.4, 91.9, 68.5, 63.7, 61.7, 47.6, 39.0, 33.0. HRMS (ESI$^+$) *m/z*=492.1024 $[M+H]^+$ found, $C_{23}H_{27}NO_3^{127}INa^+$ required 492.1030.

*4.2.20. Synthesis of macrocycle **(20)**.* To a degassed solution of **49** (34.3 mg, 73.9 μmol) in $CH_2Cl_2$ (125 mL) was added PTSA.$H_2O$ (15.2 mg, 79.9 μmol) under an argon atmosphere. The reaction was subsequently refluxed at 55 °C for 1 h after which was added Hoveyda–Grubbs second generation catalyst (4.5 mg, 7.21 μmol) followed by stirring for 72 h. The solution was degassed a second time and to the solution was added Hoveyda–Grubbs second generation catalyst (6.3 mg, 7.39 μmol) under an argon atmosphere. The reaction was subsequently reluxed at 55 °C for 16 h. The reaction was quenched with $NaHCO_3$ (30 mL) and the solvent removed under reduced pressure. The aqueous layer was extracted with $CH_2Cl_2$, after which the organic phases were combined, washed with brine (30 mL) and dried ($MgSO_4$). The crude product was purified by flash column chromatography, eluting with 30% EtOAc in petroleum ether 30–40 to yield the title compound as a colourless oil (9.0 mg, 26%). TLC $R_f$=0.25 (PE 30-40/EtOAc 7:3). $[\alpha]_D^{20}$ +37.1 (*c* 1.0, $CHCl_3$). IR $\nu_{max}$ (neat)/cm$^{-1}$: 2921 w (C–H str), 1728 s (C=O str), 1600 w (C=C str), 1586 w (C=C str). $^1$H NMR (500 MHz, $CDCl_3$): δ 7.56 (2H, d, *J* 8.2 Hz, ArH), 7.23 (1H, td, *J* 7.9, 1.5 Hz, ArH), 7.11 (1H, dd, *J* 7.3, 1.8 Hz, ArH), 6.93–6.89 (2H, m, ArH), 6.87 (2H, d, *J* 8.2 Hz, ArH), 5.98–5.91 (1H, m, $-CHCH-$), 5.79–5.73 (1H, m, $-CHCH-$), 4.50 (1H, dd, *J* 10.4, 6.7 Hz, $-CH_2-$), 4.40 (1H, dd, *J* 10.7, 7.9 Hz, $-CH_2-$), 4.22–4.13 (2H, m, $-CH_2-$), 3.82 (1H, d, *J* 12.5 Hz, $-CH_2-$), 3.62 (1H, d, *J* 12.5 Hz, $-CH_2-$), 3.35 (1H, t, *J* 6.7 Hz, –CH–), 2.90 (1H, dd, *J* 13.7, 6.4 Hz, $-CH_2-$), 2.83 (1H, dd, *J* 13.7, 7.0 Hz, $-CH_2-$), 2.56–2.40 (2H, m, $-CH_2-$). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 173.2, 157.3, 137.4, 127.7, 137.3, 133.9, 131.3, 130.9, 128.7, 126.2, 121.2, 112.4, 91.8, 62.6, 62.3, 60.9, 47.6, 38.6, 27.9. HRMS (ESI$^+$) *m/z*=464.0740 $[M+H]^+$ found, $C_{21}H_{23}NO_3^{127}I^+$ required 464.0723.

*4.2.21. Synthesis of 2-(but-3-en-1-yloxy)trans-cinnamic acid **(50)**.* To a stirred solution of **48** (1.18 g, 6.76 mmol) in toluene (120 mL) was added malonic acid **(9)** (780 mg, 7.45 mmol), pyridine

(610 μL, 7.57 mmol) and piperidine (160 μL, 1.62 mmol). The solution was refluxed at 120 °C with a Dean–Stark apparatus for 20 h. The reaction was quenched with 3M HCl and the solvent removed under reduced pressure. $H_2O$ (50 mL) was added and the aqueous layer extracted with EtOAc (2×50 mL). The organic layers were combined, washed with brine (50 mL), dried ($Na_2SO_4$) and the solvent removed under reduced pressure. The crude product was purified with flash column chromatography, eluting with a gradient from 20% to 30% EtOAc in hexane and then with 10% MeOH in EtOAc to yield the title compound as an amorphous orange solid (943 mg, 64%). Mp 78–80 °C. TLC $R_f$=0.25 (Hexane/EtOAc 7:3). IR $\nu_{max}$ (neat)/$cm^{-1}$: 2917 w br (O–H str), 1677 s (C=O str), 1619 s (C=C str), 1596 s (C=C str), 1491 m (C=C str), 1475 m (C=C str) $^1$H NMR (500 MHz, $CDCl_3$): δ 8.08 (1H, d, *J* 16.2 Hz, –*CH*CH–), 7.52 (1H, dd, *J* 7.6, 1.5 Hz, ArH), 7.35 (1H, ddd, *J* 8.2, 7.6, 1.8 Hz, ArH), 6.97 (1H, t, *J* 7.6 Hz, ArH), 6.92 (1H, d, *J* 8.2 Hz, ArH), 6.60 (1H, d, *J* 16.2 Hz, –CHC*H*–), 5.93 (1H, ddt, *J* 17.1, 10.0, 6.7 Hz, –*CH*$CH_2$–), 5.23 (1H, dq, *J* 17.4, 1.8 Hz, –$CHCH_2$–), 5.16 (1H, dq, *J* 10.4, 1.8 Hz, –$CHCH_2$–), 4.11 (2H, t, *J* 6.4 Hz, –$CH_2$–), 2.63 (2H, tq, *J* 6.7, 1.5 Hz, –$CH_2$–). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 172.2, 157.9, 142.5, 134.1, 131.8, 129.6, 123.2, 120.8, 117.8, 117.6, 112.1, 67.7, 33.7. HRMS ($ESI^+$) *m/z*=219.1009 $[M+H]^+$ found, $C_{13}H_{15}O_3^+$ required 219.1016.

*4.2.22. Synthesis of amide **(51)**.* **28** (222 mg, 1.02 mmol) and **50** (267 mg, 1.22 mmol) were dissolved in EtOAc (10 mL) at rt and then cooled to 0 °C. To this solution was added DIPEA (838 μL, 4.81 mmol) and a solution of 50% T3P in EtOAc (970 μL, 1.63 mmol). The solution was stirred at 0 °C for 30 min and rt for 18 h. The reaction was quenched with $H_2O$ (100 mL) and EtOAc (100 mL) was added. The organic layer was separated and washed with 5% $NaHCO_3$ (2×100 mL), 5% citric acid (100 mL) and then brine (70 mL). The organic extract was dried ($MgSO_4$) and the solvent removed under reduced pressure to yield the title compound as a colourless oil (280 mg, 72%). TLC $R_f$=0.72 (PE 30-40/EtOAc 4:6). $^1$H NMR (500 MHz, DMSO-$d_6$, 120 °C): δ 7.68 (1H, d, *J* 15.5 Hz, –*CH*CH–), 7.61 (1H, d, *J* 7.9 Hz, ArH), 7.33 (1H, t, *J* 8.2 Hz, ArH), 7.12 (1H, d, *J* 15.8 Hz, –CHC*H*–), 7.07 (1H, d, *J* 8.2 Hz, ArH), 6.99 (1H, t, *J* 7.8 Hz, ArH), 6.00–5.89 (1H, m, –$CHCH_2$), 5.20 (1H, d, *J* 17.3 Hz, –$CH_2$–), 5.11 (1H, d, *J* 10.1 Hz, –$CH_2$), 4.26–4.10 (5H, m, –$CH_2$–), 3.92 (1H, d, *J* 12.9 Hz, –$CH_2$–), 3.32 (1H, t, *J* 9.1 Hz, –$CH_2$–), 3.27–3.19 (1H, m, –$CH_2$–), 2.61–2.48 (6H, m, –$CH_2$–, –CH– & –CH), 2.06–1.98 (1H, m, –$CH_2$–), 1.82–1.71 (2H, m, –$CH_2$–), 1.55–1.45 (1H, m, –$CH_2$–). $^{13}$C NMR (125 MHz, DMSO-$d_6$, 120 °C): δ 172.7, 165.9, 157.6, 136.7, 135.1, 130.9, 129.2, 125.1, 121.3, 120.1, 117.2, 113.8, 81.0, 72.0, 68.5, 62.4, 45.8, 44.4, 41.6, 33.5, 27.2, 24.4, 19.0. HRMS ($ESI^+$) *m/z*=404.1848 $[M+Na]^+$ found, $C_{23}H_{27}NO_4Na^+$ required 404.1838.

*4.2.23. Synthesis of macrocycle **(21)**.* To a stirred solution of **51** (205 mg, 537 μmol) in $CH_2Cl_2$ (313 mL) was added Grubb's second generation catalyst (45.0 mg, 53.0 μmol). The solution was subsequently degassed and refluxed at 55 °C for 2 h under an ethylene atmosphere. To this solution was added Grubb's second generation catalyst (90.0 mg, 106 μmol), after which the solution was degassed and refluxed at 55 °C for 28 h under an argon atmosphere. The solvent was removed under reduced pressure and the crude product purified with flash column chromatography, eluting with 30% EtOAc in hexane to yield the title compound as a brown crystalline solid (64.9 mg, 32%). TLC $R_f$=0.26 (Hexane/EtOAc 4:6). IR $\nu_{max}$ (neat)/$cm^{-1}$: 2933 w (C–H str), 1722 s (C=O str), 1641 s (C=O str), 1598 s (C=O str), 1489 m (C=C str). $^1$H NMR (500 MHz, DMSO-$d_6$, 120 °C): δ=7.64 (1H, d, *J* 15.8 Hz, –*CH*CH–), 7.53 (1H, d, *J* 7.8 Hz, ArH), 7.32 (1H, t, *J* 7.3 Hz, ArH), 7.11–7.06 (2H, m, ArH), 6.98 (1H, t, *J* 7.3 Hz, ArH), 6.19 (1H, d, *J* 15.8 Hz, –CHC*H*-), 6.02 (1H, dt, *J* 15.8, 6.9 Hz, –*CH*CH–), 5.01 (1H, s, –$CH_2$), 4.93 (1H, s, –$CH_2$) 4.28–4.16 (4H, m, –$CH_2$–), 4.12–4.07 (1H, m, –$CH_2$–), 3.80–3.74 (1H, m, –$CH_2$–), 3.50–3.42 (1H, m, –$CH_2$–), 3.41–3.34 (1H, m, –$CH_2$–), 2.66–2.56 (3H, m, –$CH_2$– & –CH–), 2.51–2.47 (2H, m, –$CH_2$–), 1.99–1.92 (1H, m, –$CH_2$–), 1.86–1.80 (1H, m, –$CH_2$–), 1.75–1.67 (1H, m, –$CH_2$–), 1.55–1.48 (1H, m, –$CH_2$–). $^{13}$C NMR (125 MHz, DMSO-$d_6$, 120 °C): δ 172.9, 166.0, 157.8, 143.1, 136.8, 133.7, 130.7, 129.7, 127.7, 125.5, 121.4, 120.8, 115.5, 114.0, 69.0, 64.0, 46.4, 43.7, 41.2, 32.3, 31.2, 26.2, 23.0. HRMS ($ESI^+$) *m/z*=382.2018 $[M+H]^+$ found, $C_{23}H_{28}NO_4^+$ required 382.2018.

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Data accessibility: all data supporting this study are provided as Supplementary data accompanying this paper.

## Supplementary data

Supplementary data (Copies of $^1$H NMR and $^{13}$C NMR spectra) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.10.061.

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